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Epidemiology of the U.S. opioid crisis: the importance of the vector

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The roots of the remarkably lethal U.S. opioid crisis are complex and inextricably entangled with healthcare, especially in its treatment of another serious health problem: pain. Failures of the healthcare system—including lack of both training in pain management and caution in using an addictive class of medications—precipitated the rise in opioid misuse and addiction over the past two decades, but a wider range of social and economic forces has helped perpetuate the crisis and altered its character. The classic epidemiologic host-agent-environment triad can be augmented for the purpose of elucidating the current opioid crisis by addition of the “vector” to emphasize the importance of purveyors of opioids (licit and illicit), leading to our proposing an expanded host-agent-vector-environment model. Interventions addressing multiple components are needed, including solutions that account for behaviors of all vectors associated with the crisis. For prescription opioids, the vectors include clinicians and pharmaceutical-related companies involved in marketing, prescribing, distributing, and dispensing opioid medications; for illicit opioids, they include drug manufacturing and distribution networks. Attending to the vectors of opioids, while simultaneously implementing a full range of public health, clinical, law enforcement, and other approaches to ending the opioid crisis, may help to improve public health outcomes.

Keywords: opioids; epidemiology; overdose

Introduction

The U.S. opioid crisis is an extraordinary public health crisis that started at least two decades ago and has accelerated over the past decade.¹ It is a significant driver of an unprecedented downturn in life expectancy among Americans.^{2,3} In 2017 alone, 47,600 people died from an overdose involving opioids in the United States.⁴ In addition, the economic cost of the crisis in the United States is estimated at more than \$500 billion per year.⁵

Although involving compounds that are closely similar in their pharmacologic properties, the opioid crisis in the United States is really two sets of intertwined issues: misuse of and addiction to prescription opioid analgesics, which predominated in the first decade of the crisis, and, more recently, use of and addiction to illicit opioids (Fig. 1). Within the rubric of illicit opioid use, a further distinction can

be drawn between the resurgent use of heroin and the problem of both deliberate and unintentional use of even more potent synthetic opioid drugs (namely, illicitly made fentanyl and its analogs). A rapid rise in deaths involving these synthetic opioids, beginning in 2013, marked a third wave of the opioid crisis.⁶ From 2010 to 2017, deaths from fentanyl and other synthetic opioids increased nearly 10-fold, from around 3007 (14.3% of opioid-related deaths) to 28,466 (59.8%).^{4,6} Synthetic opioids are now almost twice as commonly involved in overdose deaths as prescription opioids or heroin.⁴

In addition to the significant rise in mortality, opioid use has been associated with increasing morbidity. For instance, opioid-related emergency department (ED) visits increased 30% between July 2016 and September 2017.⁷ Further, the use of opioids by pregnant women, which can lead to

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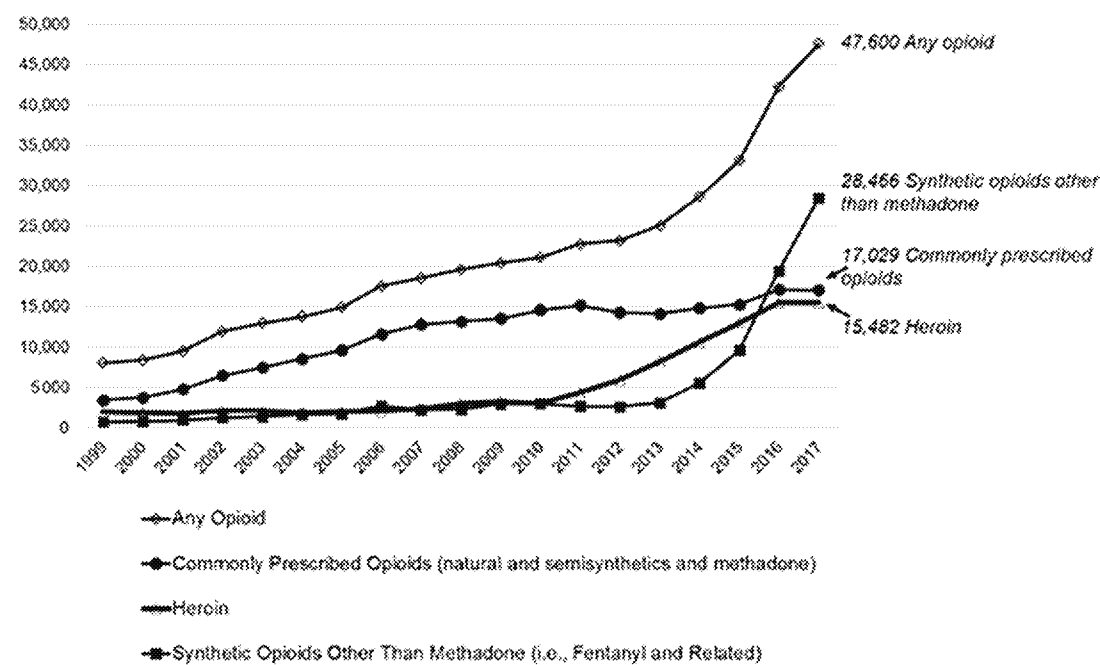


Figure 1. Opioid-related overdose death in the United States 1999–2016. (Note: categories are not mutually exclusive.) Source: National Center For Health Statistics, WONDER.

serious complications for the baby, including fetal death and infants born physically dependent on opioids (i.e., neonatal abstinence syndrome or NAS), has been increasing in recent years, as have infectious diseases from sharing infected injection drug paraphernalia. Incidence of NAS among U.S. hospital deliveries increased fourfold between 1999 and 2013 (from 1.5 to 6.0 per 1000 births).⁸

Increasing transmission of infectious diseases associated with injection drug use, in particular increasing rates of opioid injection,⁹ has been another consequence of the opioid crisis. Hepatitis C virus infections increased in the United States over the last decade, with particularly large increases in states heavily impacted by the opioid crisis.¹⁰ An HIV outbreak in Scott County, Indiana, was the most severe recent HIV outbreak in the United States, with more than 180 cases of HIV identified in a short period of time, caused by sharing of infectious syringe equipment among a network of predominantly prescription opioid-using persons.¹¹ A similar HIV outbreak associated with opioid injection in Massachusetts was recently reported.¹² In addition, CDC researchers have identified the connection between increasing rates of

invasive methicillin-resistant *Staphylococcus aureus* infections and injection drug use, including opioid injection.¹³ All of these data reflect the scope and breadth of the current opioid crisis in terms of both mortality and morbidity, and underscore the complexity of the public health, public safety, and clinical response.

Scope and epidemiology

Classic epidemiology models focus on three key components that can help to explain the spread and impact of diseases or conditions: host, agent, and environment (HAE) components. Within the *host* component are individual susceptibility factors, including genetic background and specific behaviors that may put an individual at risk. The *agent* is the external causal factor (i.e., the disease causing substance, toxin, or infectious agent) and how it operates. The *environment* encompasses factors external to the agent and host that can influence susceptibility, including both the physical and social domains. An important component of all aspects of opioid epidemiology are market forces, that is, the economic incentives that inspire both illicit sellers and licit providers of opioids and influence

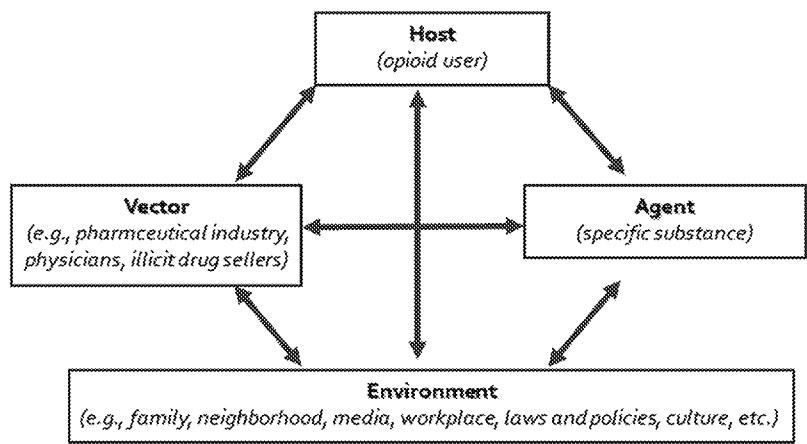


Figure 2. The host-agent-vector-environment model.

substance use patterns through their behaviors.¹⁴ To address this essential component within the typical host, agent, environment model for understanding opioid epidemiology, we include a fourth component, the *vector*. As has been described in tobacco epidemiology,¹⁵ but not previously explicated for the opioid crisis, the vector emphasizes the active role of product purveyors. For opioids, this means considering the behaviors of pharmaceutical companies and physicians (and other prescribers/dispensers) in the case of prescription opioids, as well as illicit opioid manufacturers and sellers in the case of heroin and illicitly produced synthetic opioids. These vectors contribute to and influence both the extent and spread of the opioid crisis, and must be considered when planning responses. As illustrated in Figure 2, this *host-agent-vector-environment* (HAVE) model is incorporated into the descriptions below. Adding the vector component to the epidemiologic model provides a more complete systems approach to understanding the opioid crisis than the HAE model, and explicating the bidirectional relationships among the HAVE components illustrates this point. Within the bidirectional host and vector components, for example, opioid users respond to the vector (whether illicit drug dealers or physicians writing prescriptions) by adjusting their sources of supply. Conversely, as opioid users pursue new avenues for their drugs, the vectors of opioids (both prescribers and illicit drug dealers) shift their behaviors, such that physicians may limit their prescribing and drug dealers may target a wider group of potential cus-

tomers. Each of the pairs of HAVE components can be seen as contributing similarly to a complex web of causation, with bidirectional influences across six component pairs: host and agent, host and environment, host and vector, agent and environment, agent and vector, environment and vector.

Host factors

In 2017, 11.4 million Americans (12 or older) misused opioids (defined as misuse of prescription opioids and/or use of heroin) in the past year; more than 2.1 million met criteria for a past-year opioid use disorder (OUD).¹⁶ More males than females misuse opioids; 4.7% of males (6.25 million) reported past-year misuse of opioids in 2017, compared with 3.7% of females (5.15 million). Opioid misuse and OUD have always been uncommon among adolescents, and that remains the case: in 2017, 0.6% of those aged 12–17 had an OUD. Young adults (age 18–25), however, have the highest rates of opioid misuse and OUDs, with 1.3% (445,000 people) having an OUD in 2017, compared to 0.7% of those 26 and over.¹⁶

Opioid misuse and OUD has a strong genetic component.¹⁷ Twin and family studies suggest that genetic factors are implicated in both the trajectories of drug use (i.e., from intermittent to regular use)¹⁸ and the specific onset of heroin addiction.¹⁹ Of note, inheritance of OUD may be driven by inheritance of both a general substance use disorder risk and a heritability component specific to opioids.¹⁹ Research on the specific genetic variants explaining this heritability has identified mu-opioid

receptor genetics and several other sites as promising candidates, but these and other variants only explain a small portion of the genetic variance.²⁰

Some socioeconomic factors, such as poverty, are correlated with opioid misuse.^{21–23} Nearly, 6% of those living in poverty (5.9%, 2.388 million people) misused opioids in 2017, compared with under 5% (4.8%, 2.6 million) among those between the poverty level and twice the poverty level, and just under 4% (3.9%, 6.8 million) among those who are more affluent.¹⁶ Opioid misuse also varies significantly across U.S. racial/ethnic groups.^{21–23} Opioid misuse is most prevalent among non-Hispanic whites (4.6%), less among African Americans (4.0%), and much lower among Americans of Asian heritages (1.8%).¹⁶

Mental illness, especially mood disorders, often co-occurs with OUD.^{21–23} Of the 10.4 million American adults who misused opioids in 2017, 45.9% (4.8 million) had a mental illness in the past year, and 17.1% (1.8 million) had a serious mental illness in the past year.¹⁶ The rates of co-occurring mental illness are even higher for those with a past-year OUD, with 64.3% having any mental illness in the past year and 26.9% having serious mental illness in the past year.²⁴ In 2017, 4.0% of opioid overdose deaths were categorized as intentional overdoses (i.e., suicides); however, this likely is an underestimate given the difficulties in assessing overdose death intent. According to data from the Nationwide Emergency Department Sample for the years 2006–2011, just over half of adult ED visits for opioid poisonings (53.50%) were unintentional, leaving nearly half (46.5%) as either intentional or undetermined.²⁵ In 2017, 16.8% of the adults who had misused opioids (1.7 million people) reported having serious thoughts of suicide, 6.4% (0.7 million) made suicide plans, and 3.0% (0.3 million) attempted suicide.¹⁶

As with mental illness, opioid misuse and OUD often co-occur with other substance use disorders.^{21–24} Among adults with OUD, 48.6% also had nicotine dependence, 26.4% had alcohol use disorder, 15.9% had cannabis use disorder, 15.6% had sedative/tranquilizer use disorder, 12.5% had cocaine use disorder, and 10.6% had a methamphetamine use disorder, rates which are much higher than those in persons without OUD.²⁴ Among overdose deaths, the majority of opioid-involved overdose deaths also involved mul-

tiiple drugs (or alcohol). In 2016, approximately 80% of synthetic opioid-related overdose deaths involved at least one other drug or alcohol, with heroin, cocaine, prescription opioids, and benzodiazepines being the most common co-involved substances.⁶ Such combinations, especially with respiratory depressants, such as alcohol and benzodiazepines, increase the risk of overdose.^{26–28}

OUD is also highly comorbid with pain. Chronic pain and the emotional distress associated with it may dysregulate the brain's reward and stress circuitry, raising the risk for opioid misuse and OUD.²⁹ One study estimates that 10% of patients treated for chronic pain misuse prescription opioids.²⁹ In primary care settings, the prevalence of DSM-IV defined opioid dependence (i.e., addiction) has been estimated to range from 3% to 17%.³⁰ Suicidal ideation is also common among patients with chronic pain;³¹ and overdose is the most commonly reported means of planned suicide among patients with chronic pain reporting suicidal ideation.³² Data from death investigations estimate that a minimum of 9% of suicide decedents suffered chronic pain at the time of their deaths.³³

Agent factors

Prescription opioids and illicit opioids, such as heroin and fentanyl, are pharmacologically quite similar. They interact with endogenous opioid systems that regulate several functions via three types of G protein-coupled receptors: mu, delta, and kappa. Principally, they are potent agonists at the mu receptor.³⁴ Mu-opioid receptors are particularly concentrated in areas of the brain involved in processing pain and reward. The close coupling of these two effects underlies the inherent risks of misuse of opioids when used for analgesia. Mu-opioid receptors are also concentrated in brainstem areas controlling respiration, which accounts for the life-threatening danger of overdose, as mu-opioid agonists suppress respiration.³⁵ In addition, they are found in brain circuits that handle regulating emotions, and this may contribute to their rewarding effects and to the motivation for misuse of opioids when used to help regulate mood.

It was originally thought that prescription opioid misuse and addiction was overwhelmingly confined to those using diverted prescription opioids; it was even believed that pain had a protective effect against becoming addicted to these

medications. But while it remains true that only a minority of patients with pain who receive opioids become addicted, as the volume of produced and available opioids increased in the United States, so did rates of treatment admissions for prescription opioid misuse.³⁶ Overdose risk is also not unique to patients who are misusing opioids; patients receiving opioids for pain also overdose. Multiple studies have shown that the risk of a fatal overdose rises with increased daily dose of an opioid; many of these deaths (61% in one study) may involve concurrent use of benzodiazepines, which appears to augment respiratory depression.^{26–28}

Methadone prescribed for pain has proven particularly dangerous from an overdose standpoint. Use of methadone became a popular pain-treatment option in the early 2000s because of its long half-life and the fact that it was less expensive than nongeneric extended-release opioids (such as OxyContin®). But its long half-life, slow onset of action, and complicated pharmacokinetics and pharmacodynamics make it difficult to manage medically, as well as make it particularly prone to overdose.³⁷ At its peak in the mid-to-late 2000s, methadone was involved in approximately 30% of overdose deaths, although it accounted for less than 2% of opioid prescriptions.³⁸ Methadone's role in overdose deaths has declined in recent years as prescribing it for pain has decreased;³⁷ 6.7% of opioid deaths in 2017 involved methadone.⁴ These data should remind us that the particular pharmacology of the specific opioid matters.

In addition to an increase in the absolute number of prescription of opioids during the 1990s and 2000s, *how* opioids were prescribed began to change, with opioids increasingly prescribed at higher doses, for longer durations, and in combination with benzodiazepines—all now well-recognized risk factors for overdose.^{39,40} Apart from the likelihood of dependence and the risk of addiction when opioids are given long term, there is also the real possibility that prolonged opioid administration worsens the condition it is intended to treat by *increasing* pain sensitization (hyperalgesia).⁴¹ Chronic administration of opioids may even shift the source of felt pain from the injured periphery to the central nervous system.⁴²

Illicitly made synthetic opioids generally related to fentanyl and similar compounds comprise a newer agent in the opioid crisis, as highlighted

by the marked increase in overdose deaths involving these synthetic opioids, beginning in 2013.⁶ By 2017, synthetic opioids had become almost twice as commonly involved in overdose deaths as prescription opioids or heroin.^{4,43} The exceptional potency of fentanyl—estimated at approximately 50 times more potent than heroin—helps to explain the lethality associated with this new wave of the opioid overdose epidemic.^{44–47} The combination of fentanyl and heroin, which has become prevalent in many areas of the United States, may have synergistic respiratory depressant effects.⁴⁸ Further, the proliferation of more than a dozen analogs of either fentanyl or novel synthetic opioids identified in the U.S. illicit drug market, the practice of mixing synthetic opioids with other drugs, such as cocaine or methamphetamine, and/or the pressing synthetic opioids into counterfeit tablets that look like commonly misused prescription opioids and benzodiazepines have introduced great uncertainty and unpredictability into the consequences of the illicit drug market.⁴⁹ This uncertainty and unpredictability has contributed to the sharp increase in overdose deaths in recent years.

Vector factors

Prescription opioids

Prescription drug misuse is very different from other illicit drug use issues because it is intricately intertwined with both the healthcare system and a parallel health issue affecting many Americans: pain. It was, and is, through pain suffering and the shifting philosophies of pain treatment that today's opioid crises first took root.

Physicians and other healthcare providers had learned from historical experience of the dangerous addictiveness of opioid drugs, and for decades were therefore reluctant to use them to treat most pain conditions. Beginning in the 1980s, however, there were calls from some physicians and patient advocacy groups that not enough was being done to treat pain, both in cancer and palliative-care patients, and even more generally. A now notorious one-paragraph letter in the *New England Journal of Medicine* in 1980 stated that among a large sample of hospitalized patients who had been given opioids, only four developed addiction.⁵⁰ Despite the fact that this report focused on inpatient administration of opioids, it was later cited widely to support less hesitation in using opioids in *outpatient*

settings outside of end-of-life care.⁵¹ Other small case series in the mid-1980s suggested that patients with noncancer pain, if chosen appropriately, could take opioids long term safely and with few developing misuse or addiction.⁵²

On the basis of these studies, pain advocacy organizations and some in the medical community began to seek state-based regulatory changes to reverse the perceived underuse of opioids to address chronic, noncancer pain.⁵³ These organizations successfully lobbied state medical boards and state legislatures to revise statutes and regulatory policies to enable more permissive use of opioids outside of cancer or palliative care, and to reduce the risk of sanction for prescribers who prescribed opioids. In addition, in the early 1990s, advocacy groups, including the American Pain Society, encouraged physicians to treat pain as a “fifth vital sign,” and the Joint Commission^a began to require hospitals to assess all patients’ pain. Pain rating scales became ubiquitous in doctor’s offices and emergency rooms. These clinical practice and regulatory changes coincided with business decisions that fueled a marked increase in opioid prescribing and subsequent public health harms.⁵⁴ For instance, pharmaceutical companies were developing a new generation of extended-release opioid analgesics that contained more opioid per pill but were promised to be less addicting; Purdue Pharma’s OxyContin (oxycodone) was approved and went on the market in 1996.

The marketing of OxyContin was particularly noteworthy: it included high levels of targeted outreach to primary care physicians, outreach at national meetings, incentivized sales, and even illegal sales practices, all of which fueled multibillion dollar medication sales increase starting in the 1990s.⁵⁴ These egregious practices found a particular niche in some rural areas where limited access to integrated pain treatment and high prevalence of pain conditions facilitated proliferation of prescription opioids and misuse.⁵⁴ Areas of the United States, such as Appalachia, that historically did not have much illicit opioid trade became some of the epicenters of the prescription opioid crisis. And unknown at the time, these new populations of persons with addiction to prescription-type opioid

were primed for even greater dependence and crisis from the coming influx of heroin and illicit fentanyl in subsequent years.

Shifting attitudes, marketing practices, and policies related to assessing pain occurred in the context of a medical education system that did not adequately train healthcare providers to provide state-of-the-art treatments for pain that fully incorporated concerns about opioid misuse and addiction. According to a 2011 study, many medical schools at that time offered less than 5 h of training in pain management to their students, with some offering no training.⁵⁵ Only a third of physicians felt adequately trained to manage patients with chronic pain.⁵⁶ Additionally, they lacked training in recognizing signs of medication misuse in their patients or in screening for misuse and addiction.

Opioids began to be increasingly prescribed for chronic noncancer pain, despite a lack of evidence supporting opioids’ efficacy or safety for patients with these conditions;⁵⁷ for instance, the systematic review conducted for the 2014 National Institutes of Health Pathways to Prevention^b workshop found insufficient evidence “to determine the effectiveness of long-term opioid therapy for improving chronic pain and function” but did find evidence of a “dose-dependent risk for serious harms.”⁵⁸ It also became common for patients to go home from emergency rooms, hospitals, and dental offices with prescriptions for enough opioids to last several weeks to a month to treat their acute pain, yet often needing only a few pills before their pain could be managed with over-the-counter medications.⁵⁹ As a result of these shifts in practice, the supply of prescription opioids increased fourfold between 1999 and 2010,⁵⁷ and unused pills became increasingly available for diversion and misuse. Whereas about a third of people who misuse prescription opioids get them from their own prescription, more than half report obtaining them from family or friends who have prescriptions.^{16,22,23}

The 1990s and 2000s also saw the development of rogue pain clinics (sometimes called pill mills) where opioids were prescribed and dispensed in large quantities but with few clinical indications.⁶⁰ For example, largely because of the proliferation of

^a<https://www.jointcommission.org/>

^b<https://prevention.nih.gov/research-priorities/research-needs-and-gaps/pathways-prevention>

pill mills, Florida had a well-documented prescription opioid crisis requiring a series of major policy changes in 2010 and 2011 designed to reduce the inappropriately high supply of prescription opioids. After implementing these policies, prescriptions were curtailed and the opioid overdose death rate declined 27% between 2010 and 2012.^{61,62} Obtaining prescriptions from multiple physicians (doctor shopping) also became a significant contributor to the opioid crisis and has been shown to be disproportionately associated with overdose deaths.⁶³ Interventions also have included widespread implementation of prescription drug monitoring programs (PDMPs), which are designed to alert clinicians and/or law enforcement personnel about overlapping and excess prescribing. While the evidence is mixed on their overall effectiveness, policy requirements for clinicians to use and integrate a PDMP into health delivery appear to be associated with reduced overdose risks.^{64–66}

Heroin

Marketing of heroin has also shifted with changes in both the supply countries (i.e., from Southeast Asia sources in past years to Central and South America as the predominant suppliers of the U.S. heroin market) and new sales techniques by drug dealers who took advantage of the growing population of individuals who were either misusing or had become addicted to prescription opioids.^{49,67} These millions of misusing or addicted persons, especially in the absence of adequate access to evidence-based addiction treatment, created a new market in the United States for heroin.⁶⁸ The shift from Southeast Asian heroin to, in particular, Mexican heroin facilitated the proliferation of heroin in communities across the United States through well-established drug trafficking organizations and distribution channels that had long been routes for distribution of other illicit drugs, such as cannabis and cocaine. Heroin's effects are similar to prescription opioids when the latter are taken via alternative routes of administration, such as injection; and heroin can be much less expensive than prescription opioids.

According to Muhuri and colleagues, an estimated 4% of people who misused prescription opioids initiated heroin use within the next 5 years.⁶⁹ Based on data from patients admitted to treatment programs, in the 2000s three quarters of those going to treatment for OUD had initiated misuse with

prescription opioids, even if they later switched to heroin.⁷⁰ This was in stark contrast to previous generations of people addicted to opioids, who had principally initiated with heroin. The demographics of opioid misuse and addiction also had shifted, involving a greater proportion of whites, females, and residents of suburban and rural areas than in previous decades, especially among new initiates (90% of whom were white). However, in recent years, the influx of historically high-purity and low-cost heroin in urban, suburban, and rural areas of the United States has altered this picture among patients admitted to treatment programs for OUD. Those with onset of opioid use since 2010 are again increasingly likely to report that heroin was their first opioid of misuse.⁷¹

While the increased difficulty of obtaining diverted prescription opioids among people addicted to them appears to have contributed to expanded heroin use, market forces, related to illicit drug trafficking, have also played an enormous role. As described by journalist Sam Quinones in *Dreamland*, Mexican drug cartels were ready to satisfy the demand of the emerging market for illicit opioids by using new, “pizza delivery”-like ways of marketing heroin to potential suburban buyers who otherwise might have been frightened to engage with the illicit drug trade.⁶⁷ Previously, heroin markets have been described as primarily urban in nature;⁷² however, the recent work has suggested increasing marketing in suburban and rural areas.⁷³ Techniques to facilitate sales have included sophisticated market structures, established branding of particular product batches, providing free samples, and varied pricing.^{14,73} Increased drug trafficking in areas with historically high demand for prescription opioids has also been noted.⁴⁹

Recently, intercepted heroin made from poppies grown in Mexico has been shown to be of higher purity than heroin samples available previously.⁴⁹ Unlike in past decades, this higher purity means, among other things, that intoxication can be achieved with insufflation and smoking, thereby facilitating heroin initiation and use in a more acceptable way (i.e., without injection being necessary as the initial route of administration).⁷⁴ Nevertheless, the majority of individuals using heroin eventually transition to injection use, raising their risk for overdose and infectious disease

transmission.⁷⁵ The relatively lower price of heroin (and now fentanyl, as described below) compared with prescription opioids may also have contributed to the transition from prescription opioids to heroin and other illicit opioids.⁷⁶ Prior research found that for every \$100 dollar decrease in the price per pure gram of heroin in the United States, the number of heroin overdose hospitalizations increased by nearly 3%.⁷⁷ Market factors may have even contributed to increasing heroin-related soft-tissue infections because of the influence of market factors on price and type of heroin that is used in a particular location.⁷⁸

Fentanyl and related synthetic opioids

Being synthesized in a laboratory makes fentanyl and its analogues relatively inexpensive to make and results in a substantially higher profit margin than heroin.⁴⁹ Fentanyl and its analogues are often manufactured in China and then smuggled into the United States either via the mail and express consignment systems or across the southern and northern borders via traditional drug trafficking organizations.⁴⁹ The use of the dark web and virtual cryptocurrencies, in addition, enables a relatively anonymous environment, where these drugs can be sold and purchased by individuals, and where small, independent criminal networks that are not tied to traditional drug trafficking organizations, enabling increased access to these high potency drugs at the local level and within drug-using networks.⁴⁹ The high potency of these compounds makes them particularly attractive to drug dealers and smugglers because a high street value is realized with relatively small quantities, reducing risks related to transit and trafficking compared with equipotent quantities of drugs such as heroin. The high level of potency also helps to explain their lethality. According to law enforcement sources, fentanyl compounds are increasingly packaged and sold as “heroin” by drug dealers.^{73,79} Prices of the adulterated drug may be cheaper than heroin itself and the increased potency may even be a selling point, despite the clear risk for overdose.⁷³ Dealers often adulterate heroin with synthetic opioids, as well as adulterate other illicit drugs (e.g., cocaine, methamphetamine, counterfeit prescription analgesics, and benzodiazepines) with fentanyl and related synthetic opioids, extending the risk for opioid overdose beyond people who knowingly use opioids.^{73,80} Indeed, the per-

centage of overdose deaths, involving either cocaine or psychostimulants and synthetic opioids, has been rapidly increasing.⁶

A key question is how much do people who use drugs actively seek fentanyl versus how much is surreptitiously added to the drug supply? While unintentional ingestion is certainly common, it appears that fentanyl is actively sought by some individuals who use drugs, and the high potency, as indicated by overdoses, may encourage the use of particular drug supplies.^{6,79-82} A study in New Hampshire interviewed people who use opioids about their practices and attitudes toward heroin versus fentanyl found that 25% specifically sought fentanyl or heroin laced with fentanyl over other opioids.⁸¹ While many other users preferred heroin or a specific prescription opioid, the study found that alternatives without fentanyl were hard to obtain in their region. According to Mars *et al.*,⁷⁹ evidence suggests that fentanyl has been added to the drug supply primarily because of supply-led factors, that is, fentanyl augmented sometimes expensive and/or unavailable heroin and prescription opioids in a complex drug market. Given that how rapidly, and with such devastating effects, synthetic opioids have overtaken heroin and prescription-type opioids, it is imperative that the public health community remains vigilant to market developments. The cost efficiencies and small volume of synthetic opioid products will likely continue to drive changes in drug use behavior and outcomes. The latest data from the U.S. Drug Enforcement Administration indicate an expansion and westward shift of fentanyl and fentanyl analogs in recent years;⁸³ however, it remains to be seen how completely synthetic opioids will supplant other opioids in the illicit markets over the next few years. At a minimum, strengthening partnerships between law enforcement and public health may provide important data to inform health interventions.

Environmental factors

There is significant geographic variability in the rates of drug overdose (see Fig. 3) and in opioid misuse and OUD,¹⁶ suggesting the importance of the environment in determining the population impact of opioids. This variation is associated with a range of demographic and structural factors, including healthcare infrastructure, opioid prescribing, treatment availability, availability of

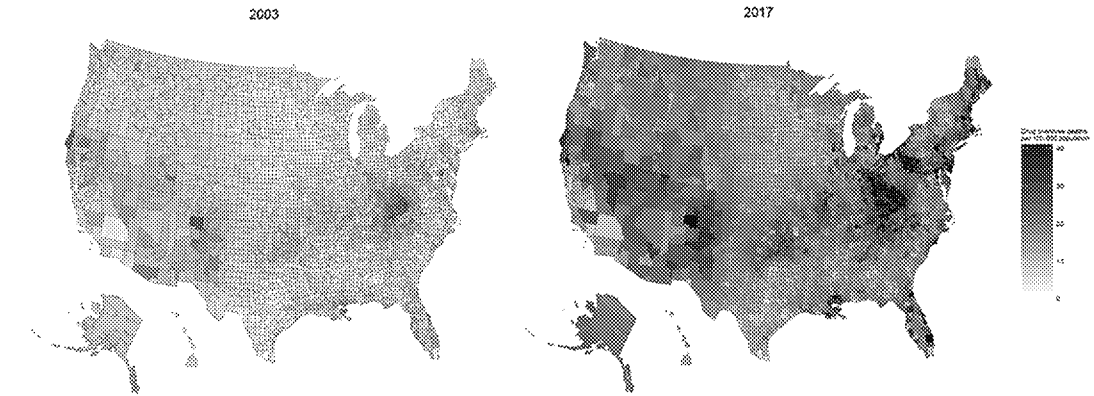


Figure 3. Estimated age-adjusted death rates per 100,000 for drug poisoning (overdose) by county in the United States, 2003 and 2017. Source: National Center for Health Statistics, National Vital Statistics System, mortality data, <http://www.cdc.gov/nchs/deaths.htm>.¹¹²

naloxone, and penetration by drug traffickers. For example, while there were 8.1 drug overdose fatalities per 100,000 persons in Nebraska in 2017, there were 46.3 per 100,000 persons in Ohio and 57.8 per 100,000 in West Virginia.⁴ The geographic distribution of illicitly-made synthetic opioids helps to explain some of the differences in overdose death rates across states in recent years. For example, the proliferation of illicitly-made synthetic opioids has disproportionately impacted states in the eastern part of the United States because of differences in underlying heroin markets. Since 2013, the majority of illicitly-made fentanyl and fentanyl analogs have been concentrated in states east of the Mississippi, where powder heroin, the predominate form of heroin, is more amenable to mixing with powder fentanyl than is black tar heroin, which is historically found in the western United States.^{49,84} In a study of the variation in NAS across counties of the United States, Patrick and colleagues documented the impact of structural environmental factors on NAS, such as long-term unemployment and mental health clinician shortages.⁸⁵ Case and Deaton suggest that broad-based, intergenerational, cumulative disadvantage may be an important contributor to the increases in drug overdoses (along with suicides and alcohol-related mortality).³

Public health responses

Optimal public health efforts to reduce the number of deaths from opioid overdoses require approaching the problem from a range of angles, including

prevention, treatment, and harm reduction. Considering the role of the vector in the opioid crisis is also important. Given the structural impact of the health care system, addressing how pain and addiction are managed and treated is key. Anticipating how the purveyors of both licit and illicit substances will respond and adapt to the public health response, and remaining nimble as the response evolves, is also essential. The public health response should be comprehensive to address both the upstream drivers and downstream consequences of opioid misuse, use disorder, and overdose, as well as prevent a shift to use of other substances. The response should also be balanced to ensure that efforts to constrain the prescribing of opioids are implemented in tandem with both appropriate tapering protocols for patients discontinuing the use of opioids and expanded access to nonopioid pain treatments.

It has been well documented that expanded access to medications for OUD is associated with reduced overdose mortality, among other public health benefits.^{86–88} In fact, providing medications for OUD for individuals in the criminal justice system, particularly those in the high-risk postincarceration period, shows promise in reducing overdose death rates.^{89,90} Yet, the lack of available medication treatment remains a serious gap in the system of care for OUD.^{88,91,92}

A comprehensive discussion of all the public health interventions required to address the opioid crisis is beyond the scope of this review. Nevertheless, currently available evidence suggests

the importance of five critical strategies: (1) healthcare provider education, training, and guidance, including deployment of clinical tools, such as PDMPs to monitor patient controlled substance prescriptions;^{55,64–66,93–96} (2) primary prevention of substance use, including opioid misuse;^{97,98} (3) expansion of medication treatment for OUDs;^{92,99–102} (4) access to, and use of, naloxone;^{103–107} and (5) implementation and scaling of comprehensive syringe services programs and other harm reduction programs, as part of an overall effort to minimize negative health outcomes associated with opioid use and use disorder.^{94,108,109} It is also recognized that new ways to address and alleviate pain with less (or no) reliance on opioids may be an essential strategy. In fact, the National Institutes of Health Helping to End Addiction Longterm (HEAL) initiative has made this a key research goal in responding to the opioid crisis.¹¹⁰

Finally, ensuring that the overall response is attentive to the vectors of licit and illicit opioids, especially the illicit drug dealers who are outside the reach of mainstream public health interventions,¹¹¹ is an essential component of a comprehensive plan. Thus, the public health response must be implemented in tandem with public safety and supply reduction efforts that aim to interdict and reduce the availability of illicit substances, apply appropriate, evidence-based policing and criminal justice interventions, including the provision of evidence-based treatment to individuals with OUD within the criminal justice system, and bring to scale innovative public health and public safety partnerships that improve utilization of effective opioid prevention and response strategies.

Conclusions

The opioid crisis that has unfolded and evolved in the United States over the first two decades of the 21st century has been remarkably lethal. The roots of the opioid crisis are complex and inextricably entangled with the healthcare system, especially in relation to treatment of the serious health problem of pain management. Although failures of the healthcare system, such as lack of training in pain management and of caution in using a class of medications known to be addictive, precipitated the rise in opioid misuse and addiction over the past two decades, a wider range of social and economic forces has helped perpetuate the crisis

and has altered its character, including multiple drug crisis involving addictive compounds that are closely related chemically but require different yet coordinated responses. The classic epidemiologic host–agent–environment triad can be augmented with the addition of the vector as a way to emphasize the importance of the purveyors of opioids (licit and illicit) in the current opioid crisis and to elucidate a full host–agent–vector–environment model of the epidemiology of, and inform the response to, the opioid crisis. Interventions addressing multiple components are needed, including solutions that account for behaviors of vectors of all types. For prescription opioids, vectors include clinicians and pharmaceutical-related companies involved in marketing, prescribing, distributing, and dispensing opioid medications; for illicit opioids, they include illicit drug manufacturing and distribution networks. Attending to all vectors of opioids while simultaneously implementing the full range of public health, clinical, law enforcement, and other approaches to the opioid crisis will likely help to improve public health outcomes.

Author contributions

W.M.C. initially drafted the manuscript, which was then jointly critically reviewed, revised, updated, and finalized by both authors. Both authors assume full responsibility for the content.

Disclaimers

The findings and conclusions of this study are those of the authors and do not necessarily reflect the views of the National Institute on Drug Abuse of the National Institutes of Health, the Centers for Disease Control and Prevention, or the U.S. Department of Health and Human Services.

Competing interests

W.M.C. reports ownership of stock in General Electric, 3M, and Pfizer Inc. unrelated to the submitted work.

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